

What is claimed is:

1. A method for detecting a molecule at an interface, which comprises labeling the molecule with a second harmonic-active moiety and detecting the labeled molecule at the interface using a surface selective technique.
2. The method of claim 1, wherein the surface selective technique is second harmonic generation or sum-frequency generation.
3. The method of claim 1, wherein the molecule is a protein, a nucleic acid, a lipid, or a carbohydrate.
4. The method of claim 3, wherein the nucleic acid is a ribonucleic acid (RNA) or a deoxyribonucleic acid (DNA).
5. The method of claim 1, wherein the molecule is a pollutant.
6. The method of claim 1, wherein the molecule is on a surface of a nanoparticle or a polymer bead.
7. The method of claim 1, wherein the second harmonic-active moiety is bound to the molecule by a specific interaction or a non-specific interaction.

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8. The method of claim 7, wherein the specific interaction comprises a covalent bond or a hydrogen bond.

5 9. The method of claim 7, wherein the non-specific interaction comprises an electrostatic interaction.

10 10. The method of claim 1, wherein the second harmonic-active moiety is specific for an amine group or a sulfhydryl group on the molecule.

15 11. The method of claim 1, wherein the second harmonic-active moiety comprises a plurality of individual second harmonic-active labels which each have a nonlinear susceptibility and are bound together in a fixed and determinate orientation with respect to each other so as to increase the overall nonlinear susceptibility of
20 the second harmonic-active moiety.

25 12. The method of claim 1, wherein the interface is at a membrane, a liposome, a cell surface, a viral surface, a bacterial surface, or a biosensor.

30 13. The method of claim 1, wherein the interface is a vapor-liquid interface, a liquid-liquid interface, a liquid-solid, or a solid-solid interface.

14. The method of claim 13, wherein the vapor-liquid interface is an air-water interface.

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15. The method of claim 13, wherein the liquid-liquid interface is an oil-water interface.
- 5 16. The method of claim 13, wherein the liquid-solid interface is a water-glass interface or a benzene-SiO₂ interface.
- 10 17. Use of the method of claim 1 to detect binding of a protein to a receptor on a membrane.
18. Use of the method of claim 1 to detect binding of a virus to a cell.
- 15 19. Use of the method of claim 1 to study protein-protein interaction at an interface.
- 20 20. Use of the method of claim 1 to study cell-cell interaction.
21. A method for detecting a molecule in a medium, which comprises:
- 25 (a) labeling a surface with a second harmonic-active moiety wherein the second harmonic-active moiety specifically interacts with the molecule to be detected;
- (b) exposing the surface to the medium thereby creating an interface at the surface,
- 30 (c) detecting the second harmonic-active moiety at the interface by measuring a signal

generated using a surface selective technique, and

(d) detecting a change in the signal when the molecule interacts with the second harmonic-active moiety, thereby detecting the molecule in the medium.

22. The method of claim 21, wherein the surface is on a nanoparticle or a polymer bead.

23. The method of claim 21, wherein the surface selective technique is second harmonic generation or sum-frequency generation.

24. The method of claim 21, wherein the molecule is a pollutant or a charged species.

25. The method of claim 24, wherein the pollutant is lead or polychlorinated biphenyl.

26. The method of claim 24, wherein the charged species is a chloride ion.

27. The method of claim 21, wherein the interaction between the second harmonic-active moiety and the molecule is an antibody-antigen interaction.

28. The method of claim 21, wherein the medium contains an amount of the molecule to be detected, the change in the signal when the molecule interacts with the second harmonic-active moiety is a quantitative change, and the

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amount of the molecule in the medium can be determined from the change in the signal.

29. A method for determining the orientation of a molecular species within a planar surface, which comprises:

(a) labeling the species with a second harmonic-active moiety which specifically binds to the species;

(b) determining the orientation of the second harmonic-active moiety with respect to the species;

(c) measuring the polarization of second-harmonic light to determine the orientation of the second harmonic-active moiety with respect to the planar surface; and

(d) determining the orientation of the species within the planar surface from the orientation of the moiety with respect to the surface as determined in step (c) and from the orientation of the moiety with respect to the species as determined in step (b).

30. The method of claim 29, wherein the orientation of the second harmonic-active moiety with respect to the species is determined using x-ray crystallography.

31. The method of claim 29, wherein the planar surface is selected from the group consisting of an organic material surface, an inorganic material surface, a polymeric material surface, a

mineral surface, a clay surface, a biological membrane surface, and a synthetic membrane surface.

- 5 32. The method of claim 29, wherein the molecular species is selected from the group consisting of an organic species, an inorganic species, a polymeric species, a protein, a lipid, a nucleic acid, and a carbohydrate.

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